Counterpoint: Selective Screening for Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance first diagnosed during pregnancy (1), is a common medical complication of pregnancy, affecting 1.1–14.3% of pregnant women depending on the ethnic and clinical characteristics of the population and the diagnostic test employed (2). Ever since O'Sullivan and Mahan (3) published their criteria for diagnosis of GDM using a 100-g oral glucose tolerance test (GTT), clinicians worldwide have been struggling to determine whether screening for GDM should be offered routinely in pregnancy and, if so, the optimal method of screening. There have been no adequately designed randomized controlled trials to answer the question of whether screening for GDM is both beneficial and cost effective, leading to a wide variance in screening practices worldwide. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), a multicenter randomized controlled trial of GDM treatment versus routine prenatal care, found a reduction in a composite of severe perinatal outcomes in the treatment group compared with a control group receiving routine prenatal care (4). Although it was not a trial of screening, its results have convinced many practitioners to adopt some type of screening for GDM because logically, in order to treat GDM (an asymptomatic entity), one must first screen for it. Recently, the U.S. Preventive Services Task Force (USPSTF), in an update to its policy statement on screening for GDM, recognized that treatment of GDM after 24 weeks of gestation improves some maternal and neonatal outcomes but, conversely, also stated that there is still insufficient evidence to support screening of all pregnant women either before or after 24 weeks of gestation (5). Despite this, most clinicians use some method of screening for GDM.

Ideally, the chosen screening protocol should identify subjects at maximal risk of adverse pregnancy outcomes who would most benefit from intensified management and surveillance, while freeing the rest from the burden of excessive interventions. Unfortunately, the policy of universal or near-universal screening that is recommended by numerous professional medical organizations (1,6–8) will lead to the blanket labeling of a large group of women as having GDM, without differentiating between those at high and those at low risk of pregnancy complications. It has very clearly been shown that glucose intolerance in pregnancy is not a threshold phenomenon but, rather, is linked to several adverse pregnancy outcomes along a continuum of measured glucose values in both fasting and postprandial (or glucose challenge) states (9–11). Not all of these outcomes are of equal clinical importance; to justify widespread screening, one would prefer to show a reduction in serious outcomes such as perinatal death and permanent birth injury. These are rare outcomes and, thus, are difficult to study. The best prospective data on the effect of increasing levels of glucose intolerance in pregnancy come from the Toronto Tri-Hospital Gestational Diabetes Project (9) and have been confirmed by the recently published results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. The data from the Toronto Tri-Hospital Gestational Diabetes Project showed a graded increase in the risk of macrosomia and preeclampsia, the need for phototherapy, and maternal and neonatal length of stay. The HAPO study largely confirmed these data and Pederson's hypothesis (12), showing a positive association between plasma glucose values after a 75-g oral GTT, birth weight above the 90th percentile, and cord blood C-peptide levels (11). Neither of these studies was able to identify clear outcome-based thresholds that could lead to new clinically relevant diagnostic criteria for GDM.

This brings us to the current status in 2009 where we have evidence that treatment of GDM reduces some perinatal outcomes without significantly increasing the cesarean section rate but still lack a gold standard diagnostic or screening test. In North America, the most common method of screening is a two-stage test comprised of a 50-g oral glucose challenge test (GCT) at 24–28 weeks of gestation followed by either a 75-g or a 100-g oral GTT for women who screen positive on the GCT (13). Using a cutoff of 7.8 mmol/l (140 mg/dl) for the GCT, ~14–18% will test positive and need to proceed to the diagnostic test. The reported sensitivity and specificity of this test strategy are ~80 and 90%, respectively, whereas the positive and negative predictive values vary according to the prevalence of GDM in the population tested (14). Thus, with this strategy some 20% of women with GDM will remain undiagnosed even with universal screening. In many parts of Europe, a risk factor–based approach to GDM screening is still the most common approach (15–17). Common risk factors can be found in Table 1. Overall, the performance of risk factor–based screening has been poor, with reported sensitivity and specificity of 63 and 56%, respectively (18). This poor performance is in part due to the inability to apply historic obstetric risk factors to women during their first pregnancy; thus, primiparas who develop GDM will likely remain undiagnosed unless they develop macrosomia, glycosuria, or polyhydramnios during the index pregnancy. The pragmatic utility of applying risk factor–based screening will largely depend on the frequency of these risk factors in the screened population. For example, if the screened population is mostly slim young Caucasians, then many women will be spared biochemical screening. On the other hand, in heavier, older, multiethnic obstetric populations, applying risk factor–based screening will likely lead to the majority of women undergoing biochemical screening. Studies from North America have shown that using the American Diabetes Association criteria for selective screening based on risk factors will lead to some 90% of the obstetric population still undergoing some form of biochemical screening (19). This leaves us with the question of whether it is possible to apply a form of risk factor–based screening that will spare the lower-risk population unnecessary tests while maintaining the performance of a universal screening protocol. The answer is available from a secondary analysis of data from the Toronto Tri-Hospital Gestational Diabetes Project (20). The subject population in-

Table 1—*Risk factors for GDM*

Current pregnancy
Age (different thresholds)
BMI (different thresholds)
Race/ethnicity
Polyhydramnios
Suspected macrosomia
Historical
GDM in previous pregnancy
Macrosomia in previous pregnancy
Unexplained stillbirth
Medical/familial
Type 2 diabetes in a first-degree relative
Polycystic ovary syndrome
Metabolic syndrome

Adapted from Berger et al., J Obstet Gynaecol Can 2002;24:894–912.

cluded a derivation group and a validation group involving 3,131 women who underwent a 50-g GCT at 26 weeks followed by a 100-g oral GTT at 28 weeks of gestation regardless of the results of the screening test. Based on the derivation group data, using multivariate analysis, a simple clinical risk scoring system was created using the clinical characteristics of maternal age, BMI, and race (Table 2). The scoring system was then applied to the validation group showing that the incidence of GDM increased with increasing clinical score values ranging from 0.9 in women who scored ≤1 to 18.7% in women who scored ≥6. A screening strategy was then developed where women with clinical scores ≤1 were not screened; women with scores 2–3 were screened, and the current cutoff of 7.8 mmol/l (140 mg/dl) was retained, whereas for women with scores ≥4, two thresholds were examined: 128 and 130 mg/dl. This strategy was then applied to the validation group with the results showing that although it achieved sensitivity and specificity similar to those associated with universal screening, selective screening allowed 34.6% of women to avoid screening altogether and maintained a detection rate of >80%. If we apply this simple strategy of asking a woman her age and ethnicity and calculating her BMI to the most recent North American birth statistics, ~1.4 million women in North America could avoid routine screening for GDM (21). Although some cases of GDM will be missed in the lower-risk category, more cases will be diagnosed in the higher-risk category as a result of the lower thresholds applied to this population. The economic analysis of this strategy has not been evaluated yet; however, assuming that the impact of not diagnosing GDM in the low-risk population is minimal in terms of health care USD, it is likely to result in savings of close to 4 billion USD per year (22,23).

Table 2—*Scoring system for GDM screening based on clinical risk factors*

Risk factors	Score
Age (years)	
≤30	0
31–34	1
≥35	2
BMI (kg/m^2)	
≤22.0	0
22.1–25	2
≥25.1	3
Race	
Caucasian	0
Black	0
Asian	5
Other	2

Adapted from Naylor et al., N Engl J Med 1997;337:1591–1596.

The main limitation of this method of selective screening is that it is more complex than universal screening and its implementation adds an additional burden to the health care provider. But what is the actual burden? The data regarding age, ethnicity, and BMI are collected routinely at the first prenatal visit. All the clinician needs to do is to determine at that point whether the patient is in the low-risk category and thus can avoid screening. For the remainder of patients who undergo a GCT, the linkage between this clinical dataset and the laboratory can easily be incorporated into the laboratory reporting system, similar to what currently occurs with prenatal screening for trisomy 21, allowing for the accurate application of different glucose threshold values based on the individual clinical scores.

In summary, there is still a wide gap between screening practices in European countries and North America. Regardless of the screening method employed, the decision whether to provide selective screening or universal screening is largely based on personal preference, expert opinion, and clinical guidelines given that there is limited supporting evidence from well-designed randomized clinical trials supporting one method over the other. Until better evidence is available, those who employ universal screening need to ask themselves whether it is justified to subject all pregnant women to GDM screening; although universal screening will arguably identify more cases of GDM in the low-risk population, these cases might have less clinical significance. By applying selective screening strategies, one can increase the detection of GDM in the higher-risk population (increased maternal age and BMI), especially if lower threshold criteria are applied to the GCT in this select population. By doing this, we will be able to focus our resources on identifying cases where making the diagnosis of GDM will have an effect on significant perinatal outcomes, while perhaps avoiding increased maternal anxiety (24) and higher cesarean section rates (25) in the low-risk population.

Howard Berger, md[1]
Mathew Sermer, md[2]

From the [1]Department of Obstetrics and Gynecology, St. Michael's Hospital, University of Toronto, Toronto, Canada; and the [2]Department of Obstetrics and Gynecology, Mount Sinai Hospital, University of Toronto, Toronto, Canada.

Corresponding author: Mathew Sermer, msermer@mtsinai.on.ca.

DOI: 10.2337/dc09-0361

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus: the Organizing Committee. Diabetes Care 1998;21(Suppl. 2):B161–B167
2. National Diabetes Data Group. *Diabetes in America*. 2nd ed. Harris M, Ed. Bethesda, MD, National Institutes of Health, 1995
3. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. Diabetes 1964;13:278–285
4. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486
5. Hillier TA, Vesco KK, Pedula KL, Beil TL, Whitlock EP, Pettitt DJ. Screening for gestational diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008;148:766–775
6. American College of Obstetricians and Gynecologists Committee on Practice

Bulletins—Obstetrics. Clinical management guidelines for obstetrician-gynecologists. Gestational diabetes. Obstet Gynecol 2001;98:525–538
7. American Diabetes Association. Diagnosis and classification of diabetes mellitus (Position Statement). Diabetes Care 2009; 32(Suppl. 1):S62–S67
8. Berger H, Crane J, Farine D, Armson A, De La RS, Keenan-Lindsay L, Leduc L, Reid G, Van AJ. Screening for gestational diabetes mellitus. J Obstet Gynaecol Can 2002;24:894–912
9. Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie JW, Farine D, Cohen HR, McArthur K, Holzapfel S, Biringer A, Chen E, the Toronto Tri-Hospital Gestational Diabetes Investigators. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes: the Toronto Tri-Hospital Gestational Diabetes Project. Am J Obstet Gynecol 1995;173:146–156
10. Tallarigo L, Giampietro O, Penno G, Miccoli R, Gregori G, Navalesi R. Relation of glucose tolerance to complications of pregnancy in nondiabetic women. N Engl J Med 1986;315:989–992
11. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008; 358:1991–2002
12. Pederson J. *The Pregnant Diabetic and Her Newborn*. Baltimore, MD, Williams & Wilkins, 1977
13. Gabbe SG, Gregory RP, Power ML, Williams SB, Schulkin J. Management of diabetes mellitus by obstetrician-gynecologists. Obstet Gynecol 2004;103:1229–1234
14. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982;144:768–773
15. Jensen DM, Molsted-Pedersen L, Beck-Nielsen H, Westergaard JG, Ovesen P, Damm P. Screening for gestational diabetes mellitus by a model based on risk indicators: a prospective study. Am J Obstet Gynecol 2003;189:1383–1388
16. Mires GJ, Williams FL, Harper V. Screening practices for gestational diabetes mellitus in UK obstetric units. Diabet Med 1999;16:138–141
17. Ostlund I, Hanson U. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. Acta Obstet Gynecol Scand 2003;82:103–108
18. O'Sullivan JB, Mahan CM, Charles D, Dandrow RV. Screening criteria for high-risk gestational diabetic patients. Am J Obstet Gynecol 1973;116:895–900
19. Danilenko-Dixon DR, Van Winter JT, Nelson RL, Ogburn PL Jr. Universal versus selective gestational diabetes screening: application of 1997 American Diabetes Association recommendations. Am J Obstet Gynecol 1999;181: 798–802
20. Naylor CD, Sermer M, Chen E, Farine D. Selective screening for gestational diabetes mellitus. Toronto Trihospital Gestational Diabetes Project Investigators. N Engl J Med 1997;337:1591–1596
21. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2005. Natl Vital Stat Rep 2006;55:1–18
22. Scott DA, Loveman E, McIntyre L, Waugh N. Screening for gestational diabetes: a systematic review and economic evaluation. Health Technol Assess 2002;6:1–161
23. Nicholson WK, Fleisher LA, Fox HE, Powe NR. Screening for gestational diabetes mellitus: a decision and cost-effectiveness analysis of four screening strategies. Diabetes Care 2005;28:1482–1484
24. Feig DS, Chen E, Naylor CD. Self-perceived health status of women three to five years after the diagnosis of gestational diabetes: a survey of cases and matched controls. Am J Obstet Gynecol 1998;178: 386–393
25. Naylor CD, Sermer M, Chen E, Sykora K. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? Toronto Trihospital Gestational Diabetes Investigators. JAMA 1996;275: 1165–1170